CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Thiamethoxam

Chemical Code # 5598, Tolerance # 52691
SB 950: not assigned

Original date 10/22/99
Revised 8/23/00

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 172709 (Document no. 52691-187) were examined. This includes all relevant studies indexed by DPR as of 8/23/00.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: t000823
R. Duncan, 8/23/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****52691-080 167773** "24-Month Carcinogenicity and Chronic Toxicity Study in Rats" (Bachmann, M. 835-Novartis Crop Protection AG, Stein, Switzerland; Study # 942110, 7/27/98). CGA-293343 Technical (Batch # P.506006, purity 98.6%) was administered in the feed to 80 Tif: RAIf(SPF) rats/sex/dose at levels of 0, 10, 30, 500 or 1500 ppm in males and 0, 10, 30, 1000 or 3000 ppm in females for 24 months. A treatment-related decrease in body weight gain was noted in females only at 3000 ppm; dose-related clinical observations were limited to slightly increased incidence of hunched posture in this group. Dose-related hematology, clinical chemistry and urinalysis changes were not indicated. At the terminal sacrifice, mean carcass weight was slightly lower for high-dose males and females (reduced by 4% and 8%, respectively). Interim sacrifice males showed increased incidences of chronic tubular lesions, basophilic proliferation and lymphocytic infiltration of the kidneys at 500 (2/10 vs. 4/10, p=0.31) and 1500 ppm (2/10 vs. 6/10, p=0.08); lymphocytic infiltration of the renal pelves was also increased in males at 1500 ppm. **Possible Adverse Effect:** Increased incidence and severity of chronic nephropathy (30/50 vs. 42/50, p<0.05) and higher incidence of lymphocytic infiltration (10/50 vs. 17/50, p<0.05) in the kidneys of high-dose males at terminal sacrifice, possibly due to a-2-microglobulin accumulation. Females show a slight increase in severity of hemosiderosis of the spleen at the 3000 ppm dose level at interim sacrifice, but not at the final sacrifice. Females at this level did show an increased incidence of foci of cellular change in the liver at terminal sacrifice (10/50 vs. 26/50, p<0.05). There were no indications of compound-related neoplastic development. **Chronic NOEL(M)=500 ppm** (21.0 mg/kg/day, based on kidney lesions). **(F)=1000 ppm** (50.3 mg/kg/day, based on liver lesions). **Acceptable.** Kellner, 9/8/99.

CHRONIC TOXICITY, DOG

****52691-060 167757** "12-Month Chronic Dietary Toxicity Study in Beagle Dogs" (Altmann, B. 831-Novartis Crop Protection AG, Stein Switzerland; Study # 942108, 7/22/98). CGA-293343 (Batch # P.506006, purity 98.6%) was administered in the feed to 4 Beagle Dogs/sex/dose at levels of 0, 25, 150, 750, 1500 ppm for 52 weeks. There were no mortalities and no compound-related clinical signs reported. Body weight gain was reduced by 26% in high-dose males over the duration of the study; a slight reduction in body weight and transient reduction in food consumption was noted in high-dose females early in the study. Reduced prothrombin activities were noted in both sexes at 1500 ppm. Dose-related increases in plasma creatinine and urea levels were reported throughout the study at 750 and 1500 ppm (both sexes). Alanine aminotransferase activity was reduced in males at 750 and 1500 ppm and lower albumin levels were noted in high-dose females. Absolute and relative testes weights were slightly reduced in two males at 1500 ppm; microscopically, this change was associated with a slight increase in the incidence and severity of tubular atrophy; **Possible Adverse Effect:** Bilateral tubular atrophy was noted in the testes of two dogs in each of the 750 and 1500 ppm dose groups. **NOEL(M/F) = 150 ppm** (M: 4.05 mg/kg; F: 4.49 mg/kg) based on bilateral tubular atrophy in males and changes in blood chemistry of both sexes at 750 and 1500 ppm. **Acceptable.** Kellner, 8/24/99.

ONCOGENICITY, RAT

See Combined Toxicity, Rat.

ONCOGENICITY, MOUSE

****52691-061**, -056, -082, -083 **167758** 167751 167700 167701 "18-Month Carcinogenicity Study in Mice" (Bachmann, M. 832-Ciba-Geigy Limited, Stein, Switzerland; Study # 942109, 6/2/98). CGA-293343 Technical (Batch # P.506006, purity 98%) was administered in the feed to 60 Tif: MAGf (SPF) mice/sex/dose at levels of 0, 5, 20, 500, 1250 or 2500 ppm for 18 months (50 mice/ sex/dose for

oncogenicity, 10/sex/dose for hematology and 10 control and high-dose mice/sex for 9 month interim sacrifice). Reductions in body weight gain resulted in significant differences in body weight in 2500 ppm males at week 7 and from week 11 onwards and in females from week 38 onwards. Clinical observations included distended abdomen in females at 1250 ppm and in both sexes at 2500 ppm. Significantly higher mean corpuscular hemoglobin (MCH) was noted for high-dose males at week 53 and 78. At terminal sacrifice, mean carcass weights were reduced in high dose males and females (-9% and -7%, respectively); absolute and relative liver weights were increased in males at 1250 ppm and above and in females at 500 ppm and above. Gross necropsy revealed increased incidences of masses and nodules in the liver of mice at 500 ppm and above and thickening of the stomach in some of the high-dose males. **Possible Adverse Effect**: significantly increased hepatocellular adenomas were noted in both sexes at 500 ppm and above. Neoplastic lesions also included increased hepatocellular adenocarcinomas in high-dose males and females and in females at 1250 ppm. Mice at 500 ppm and above also showed increased incidence of inflammatory cell infiltration, necrosis of single hepatocytes, hepatocellular hypertrophy, increased mitotic activity, deposition of pigments and hyperplasia of Kupffer cells. **NOEL (non-neoplastic lesions)=20 ppm** (M=2.63 mg/kg; F=3.68 mg/kg, based on liver pathology at 500 ppm and above). Supplementary liver studies indicated that CGA-293343 increased proliferative activity of hepatocytes at 500 and 2500 ppm, with an enzyme induction profile similar to that of the model inducer phenobarbital. **Acceptable**. Kellner, 8/11/99.

REPRODUCTION, RAT

52691-068 167771 "CGA-293343 Technical: Rat Dietary Two-Generation Reproduction Study (including Effects on Sperm Cell Parameters)" (Doubovetzky, M. 834- Novartis Crop Protection AG, Stein, Switzerland, Study# 942121 and 982015, 7/20/98). CGA-293343 technical (Batch # P.506006, purity 98.6%) was administered in the diet at 0, 10, 30, 1000 and 2500 ppm (mg/kg equivalents for F0 females at study start was 0.9, 2.8, 83.4 and 225.7 mg/kg/day for test-compound dosing dams, respectively) to 30 Tif: RAI f (SPF) rats/sex/dose (F0 mating, with two matings per generation); 30 weanlings/sex/dose from the first litters of the F0 generation were selected for the F1 mating. F0 and F1 animals were treated for 10 weeks prior to mating, and then during mating, gestation and lactation. There were no treatment-related mortalities, clinical signs or necropsy findings in the F0 and F1 adults. Body weights were slightly reduced (-7%) compared to controls in the high-dose F0 males from the premating period (weeks 5 through 9); Bodyweight of both male and female rats selected for the F1 generation were reduced at 2500 ppm. Relative organ weights for spleen, heart and liver were significantly increased in high dose group F0 males. In F1 males, increased relative spleen and liver weights were reported. Absolute and relative thymus weights were reduced at 1000 and 2500 ppm F1 females. In 1000 and 2500 ppm F0 and F1 males and one (1/30) F1 female, an increased incidence of minimal to marked hyaline change of renal tubules was noted; increased incidence of renal casts was seen in high-dose F0 males and in 1000 and 2500 ppm F1 males. **Parental NOEL(M)=30 ppm (approx. 1.3 to 4.3 mg/kg/day); **(F)=1000 ppm** (59.3 to 219.6 mg/kg/day), based on kidney lesions. In both the F0 and F1 generations, mating and viability parameters (i.e., mating, fertility, gestation, live birth, viability and lactation indices) were similar to control in all dosage groups. **No reproductive effects; Reproductive NOEL=2500 ppm** (approx. 226-515 mg/kg/day);. F2 litter weight gain showed reductions at the 1000 and 2500 ppm levels. **Developmental NOEL= 30 ppm** (1.3 to 4.3 mg/kg/day; based on reduced pup weight). **Acceptable**, Kellner, 7/29/99.

52691-070, -071 167775, 167777; "CGA-293343 Technical: Rangefinding Rat Dietary Reproduction Study" (Winkler, G., Short/Long-term Toxicology, Novartis Crop Protection, Basle, Switzerland). CGA-293343 Technical (Batch # P.506006, purity 98%) was administered in the feed to 15 Tif: RAI f (SPF) rats/sex/dose at doses of 0, 1000, 2000 and 4000 ppm beginning two weeks before mating and continuing through two weeks postpartum. There were no treatment-related mortalities or clinical signs. Body weight and body weight gain of high-dose males was reduced during premating. In females, body weight gain was reduced at all dose levels during premating; body weight was reduced during lactation in the high-dose females. Food consumption was reduced in high-dose males and mid- and high-dose females during premating. There were no effects on male and female mating and fertility indices and no changes reported for gestation and parturition indices or duration of gestation. The only compound-related change in litters was reduced litter weights (day 14) and litter weight gain between days 0 and 14

in the high dose group. Supplemental study. The addendum to the final report (-071:167777) was a copy of the protocol for the range-finding study. Kellner, 10/4/99 .

176; 171348; "CGA-293343 Technical: Rat Dietary Two-Generation Reproduction Study (including Effects on Sperm Cell Parameters), Amendments 3 and 4"; (Doubovetzky, M.; Novartis Crop Protection AG , Stein, Switzerland; Study# 942121 and 982015; 1/7/99 (Amendment 3), 7/26/99 (Amendment 4). The original reported incidence of testicular tubular atrophy in F1 males was 6/30, 8/30, 15/30, 24/30, and 14/30 (for 0, 10, 30, 1000, and 2500 ppm, respectively). In this submission, testes in all F0 and F1 males were reexamined to distinguish between minute focal tubular changes and diffuse tubular atrophy. The primary conclusion was that the difference in the 1000 ppm group remained: the incidence of diffuse tubular atrophy was 0/30, 1/30, 1/30, 7/30** ($p \leq 0.01$) , and 3/30 (for 0, 10, 30, 1000, and 2500 ppm, respectively). Historical control incidence ranged up to 10%. This is not considered a treatment-related effect because of the lack of a dose response at 2500 ppm. **Supplemental.** (Duncan, 8/22/00)

TERATOLOGY, RAT

52691-065, -066, -067 167767, 167768, 167770 "CGA-293343 Technical Rat Oral Teratogenicity"(Winkler, G. 833-Novartis Crop Protection, AG, Basel, Switzerland, Study #942118, 8/7/96). CGA-293343 Technical was administered via oral gavage to 24 pregnant Tif : RAI f (SPF) rats/dose at levels of 0, 5, 30, 200 or 750 mg/kg/day on days 6 to 15 of gestation. All surviving dams underwent cesarean sectioning on day 21 of gestation and the uteri were examined for the number and distribution of implantation sites, total resorptions and live and dead fetuses; the ovaries were examined for the number of corpora lutea. One high-dose dam was killed for humane reasons and all other dams survived to study termination; 17 other high-dose dams had dose-related hypoactive behavior, piloerection and regurgitation of test material. Mean maternal body weight gain and food consumption was significantly decreased in the mid- and high-dose groups. **Maternal NOEL =30 mg/kg/day (based on body weight effects). No significant differences in mean number of corpora lutea, implants, litter size, sex ratio or number of resorbed fetuses were seen. Mean body weights of male and female fetuses were significantly reduced in the high dose group. Compound-related skeletal anomalies in the high-dose group consisted of increased incidence of asymmetrically shaped sternebra-6 and increased irregular ossification of the occipital bone. Fetal skeletal variations (probably related to delayed ossification) consisted of increased incidences of irregular, poor or absent ossification of cranial bones, sternebra, metatarsals and phalanges and shortened ribs in the high dose group. **No Adverse Effect:** . **Developmental NOEL=200 mg/kg** (based on decreased fetal body weight and skeletal variations at 750 mg/kg). Acceptable. Kellner, 7/7/99.

TERATOLOGY, RABBIT

52691-062, -063, -064 167762, 167763, 167765 "CGA-293343 Technical: Rabbit Oral Teratogenicity" (Winkler, G. 833- Novartis Crop Protection AG, Basle, Switzerland. Study #942119, 8/13/96). CGA-293343 technical (Batch # P.506006, purity 98.6%) was administered via oral gavage to 19 artificially inseminated Russian, Chbb:HM Rabbits/dose at levels of 0, 5,15, 50 and 150 mg/kg/day on days 7 through 19 of gestation. Cesarean sectioning occurred on day 29 of pregnancy. One high-dose dam had vaginal bloody discharge on day 19 of gestation and was found dead the next day; another in this group had vaginal bloody discharge on day 18 and 19 and was sacrificed moribund on day 19. Bloody discharge in the perineal area was noted in a high-dose dam on day 22 and this dam was sacrificed the same day for severe weight loss. Body weight gain was reduced at 50 and 150 mg/kg. Food consumption was significantly reduced in these groups during the treatment period (days 7 to 12 and 12 to 16) and from day 16 to 20 in the high-dose group. Findings after necropsy included hemorrhagic contents in the uterus and vaginal hemorrhage in the dam that was found dead. The two dams that were sacrificed on days 19 and 22 also had hemorrhagic contents in the uteri **Maternal NOEL =15 mg/kg/day (based on reduced body weight gain). Dose-related increases in postimplantation losses resulting from increased early resorptions were noted in the 150 mg/kg dose group and mean fetal weights were significantly reduced at this level. Fetal skeletal evaluations revealed significant increases in fused sternebrae 3 and 4 (anomalies) at the high dose level. An increase in variations, namely absent ossification of the medial phalanx of anterior digit-5, was noted in 4 high-dose fetuses. **No Adverse Effects.**

Developmental NOEL=50 mg/kg (based on reduced fetal bodyweight at 150 mg/kg). Acceptable. Kellner, 7/13/99.

GENE MUTATION

52691-073 167691 "Salmonella and Escherichia/Mammalian-Microsome Mutagenicity Test" (Hertner, Th., 842-Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland Study #952014, 11/2/95). CGA-293343 Technical (Batch # P.506006, purity 98.6%) was tested for mutagenic potential in the Salmonella and Escherichia coli/Mammalian-Microsome Mutagenicity Assay at levels of 0, 312.5, 625, 1250, 2500 and 5000 ug/plate (triplicate plating) using strains TA98, TA100, TA 102, TA1535, TA1537 (*S. typhimurium*) and WP2uvrA (*E. coli*) with and without metabolic activation (Aroclor 1254-induced male rat liver S-9 fraction) using triplicate plating in two separate trials. Positive controls were functional. **No Adverse Effects: The test article was negative for mutagenic potential under the conditions tested. **Acceptable**. Kellner, 9/22/99.

52691-074 167692 "Gene Mutation Test with Chinese Hamster Cells V79" (Ogorek, B., 842-Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland, Study # 952015, 1/12/96). CGA-293343 Technical (Batch # P.506006, purity 98.6%) was tested for mutagenic potential in Chinese hamster V79 cells using the V79/HGPRT mutation assay with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) at dose levels in the original trial ranging from 123.33 to 3330.0 µg/ml (with S-9) and 61.67 to 1665.0 µg/ml (without S-9); levels in the confirmatory assay ranged from 416.25 to 3330.0 µg/ml (with S-9) and 277.5 to 2220.0 µg/ml (without S-9). Incubation times with CGA-293343 or control with S-9 were 5 hr; without S-9: 21 hr. **No Adverse Effects: there was no significant increase in mutant frequency at any level of CGA-293343 in the original or confirmatory trial. The test article was negative for mutagenicity under the conditions tested. **Acceptable.** Kellner, 9/23/99.

186; 172708; "*Salmonella*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland; Study No. 992020, Novartis No. 1170-99; 10/21/99); *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were treated with 312.5-5000 ug/plate CGA-293343 (thiamethoxam; purity = 98.6%; Batch No. P.506006)/DMSO with metabolic activation by mouse liver S-9 fraction from untreated mice, mice fed 50 ppm, 500 ppm, or 2500 ppm CGA-293343 in the diet for 20 d, or mice injected IP with Aroclor 1254 five days prior to sacrifice; triplicate plates/treatment, 30 mins. preincubation, one trial; **no adverse effects;** no increase in reversion rates; positive controls were functional; **Supplemental.** (Duncan, 7/31/00)

CHROMOSOME EFFECTS

52691-072 167690 "Cytogenetic Test on Chinese Hamster Cells *In Vitro*" (Zeugin, S., 843-Genetic Toxicology, Novartis Crop Protection, Basle, Switzerland, Study #952016, 6/18/96). CGA 293343 Technical (Batch # P.506006, purity 98.6%) was tested for clastogenic potential in Chinese hamster ovary cells (CCL 61) at concentrations ranging from 35.47 to 4540 ug/ml with and without metabolic activation (Aroclor 1254 induced rat liver microsomal enzyme) in two trials. In the absence of S-9 activation, cells were exposed for 21 or 45 hours (3 groups); in the presence of S-9 activation cells were exposed for 3 hours (3 groups). One-hundred metaphase spreads/duplicate flask were scored for chromosomal aberrations. Five of the six groups showed no significant compound-related increase in chromosome aberrations. In the experiment performed with metabolic activation after 3 hours treatment/42 hours recovery, the percentage of specific chromosomal aberrations was 1.0%, 1.5% and 0% at the 2270, 3405 and 4540 µg/ml concentrations, respectively. The percent specific aberrations obtained in the 3405 ug/ml dose group was statistically significantly different from the 0% value seen in the negative control group using Chi-square analysis. This probably did not represent compound-related effect (i.e., this was an isolated positive outcome in which the negative control value was unusually low). **No Adverse Effects: the test compound is negative for chromosome aberrations under the conditions tested. **Acceptable**. Kellner, 9/22/99.

**52691-075 167693 "Micronucleus Test, Mouse (OECD Conform)" (Hertner, Th., 843- Genetic Toxicology, Novartis Crop Protection, Basle, Switzerland, Project #A952018, 12/15/95). CGA

293343 Technical (Batch # P.506006, purity 98.6%) was tested *in vivo* for clastogenic activity in polychromatic erythrocytes from bone marrow in two parts: Part 1 had 13 female Tif: MAGf(SPF) mice that were administered the test compound (oral gavage) with a single dose (1250 mg/kg) at two sampling times (24 and 48 hours). In part 2, the test was performed with three doses (312.5, 625 and 1000 mg/kg) with groups at 1000 mg/kg sampled at 16, 24 and 48 hours and the remaining dose groups sampled at 24 hours only; 2000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. The positive control group received cyclophosphamide (64 mg/kg). In part 1, 7 of 13 mice were found dead after 4 to 5 hours; three females died after 48 h of treatment at 1250 mg/kg, two died after 24 h treatment and two females died in the 1250 mg/kg reserve group. Because of high female losses, dose levels for females in part 2 at the 16 hour sampling time and males at all sampling times were reduced to 1000 mg/kg. At this level, half of the mice had symptoms indicating compound-related toxicity; reduced motor activity was seen as low as 625 mg/kg. **No Adverse Effects**: In groups treated with CGA-293343, there were no dose-related increases in the number of micronucleated polychromatic erythrocytes in bone marrow cells compared to control. Acceptable. Kellner, 9/20/99.

DNA DAMAGE

52691-076 167694 "Autoradiographic DNA Repair Test on Rat Hepatocytes (OECD Conform) *in Vitro*" (Ogorek, B., 844; Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland, Study # 952017, 1/29/96). CGA-293343 Technical (Batch # P.506006, purity 98.6%) was tested for potential DNA damage (UDS) *in vitro* at concentrations of 0.0, 13.01, 52.04, 208.13, 416.25, 832.5 and 1665 µg/ml for 16-18 hours in two trials using primary rat heptocytes from male Tif.RAIf(SPF) rats. The mean net nuclear grain counts for the 416.25, 832.5 and 1665 µg/ml exposure levels were 0.5, 0.5 and 0.3, respectively, in the initial trial and 0.7, 0.6 and 0.8, respectively, in the second (confirmatory) trial. **No Adverse Effects: mean net nuclear grain counts in both trials were comparable to the mean net control value of 0.5. **Acceptable.** Kellner, 9/16/99.

NEUROTOXICITY

035, 036, 170; 167679, 167680, 170881; "Acute Neurotoxicity Study of Orally Administered CGA-293343 Tech in Rats" (Minnema, D.J., Covance Laboratories Inc., Vienna, VA, Study No. 6117-364, Novartis Nexus No. 507-96, 9/23/97). 818. CGA-293343 Technical (Batch No. 9600110, purity=98.7%), prepared in 0.5% aqueous methylcellulose, was administered by gavage in a single dose at dose levels of 0 (vehicle), 100, 500, and 1500 mg/kg to 10 Sprague-Dawley Crl:CD^{7}Br rats per sex per dose level. 3 female animals at 1500 mg/kg died during the first 2 days of the study. During FOB assessments, a treatment-related decrease in mean body temperature and treatment-related incidences of uncoordinated landing in the righting reflex test in both sexes at 500 and 1500 mg/kg approximately 2 hours post-dose were observed. Decreased locomotor activity was observed during the first 15 to 20 minutes of the 2 hours post-dose assessment in both sexes at 500 and 1500 mg/kg. FOB and locomotor activity assessments conducted 1 week and 2 weeks post-dose revealed no treatment-related effects. Microscopic examination revealed no treatment-related effects. **No adverse effects.** NOEL (M/F)=100 mg/kg (based on treatment-related decreases locomotor activity and body temperature, and uncoordinated landing in righting reflex test). **Acceptable**. (Corlett and Leung, 9/29/99)

059; 167755; "13-Week Subchronic Neurotoxicity Study with CGA-293343 Tech. in Rats" (Minnema, D.J., Covance Laboratories Inc., Vienna, VA, Study No. 6117-363, Novartis Nexus No. 772-97, 6/23/98). 827. CGA-293343 Technical (Batch No. 9600110, purity=98.7%) was admixed to the feed at dose levels of 0, 10, 30, 500, or 1500 ppm for males (0, 0.7, 1.9, 31.8 or 95.4 mg/kg/day, respectively) and 0, 10, 30, 1000, or 3000 ppm for females (0, 0.7, 2.1, 73.2, or 216.4 mg/kg/day, respectively) and fed to 10 Sprague-Dawley Crl:CD7BR rats per sex per dose level continuously for a period of at least 13 weeks. No animals died. No treatment-related clinical signs were observed. No treatment-related effects were observed during FOB and locomotor activity assessments. No treatment-related effects were observed at gross necropsy or microscopic examination. **No adverse effects**. NOEL (M)=95.4 mg/kg/day (1500 ppm) and (F)=216.4 mg/kg/day (3000 ppm) (based on no treatment-related effects at HDT). **Acceptable**. (Corlett and Leung, 9/29/99)

SUBCHRONIC STUDIES

(Oral)

054; 167749; "3-Month Oral Toxicity Study in Rats (Administration in Food)" (Bachmann, M., Novartis Crop Protection AG, Short/Long-term Toxicology, Basle, Switzerland, Study No. 942089, Novartis Nexus No. 471-94, 1/23/96). 821. CGA 293343 tech. (Batch No. KI-4654/18, purity=98.4%) was admixed to the pelleted food at dose levels of 0, 25, 250, 1250, 2500, or 5000 ppm (0, 1.74, 17.6, 84.9, 167.8, and 328.8 mg/kg/day, respectively, for males and 0, 1.88, 19.2, 92.5, 182.1, and 359.1 mg/kg/day, respectively, for females) and fed to 10 Tif:RAIf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level for a period of 90 consecutive days. No treatment-related deaths occurred. No treatment-related clinical signs were observed. Statistically significant increases in mean relative heart, liver, kidney, spleen, and adrenal weights in males at 5000 ppm were observed. Microscopic examination of males revealed treatment-related incidences of hepatocyte hypertrophy beginning at 2500 ppm, acute tubular lesions in the kidney beginning at 1250 ppm, and hyaline change in the renal tubular epithelium and chronic tubular lesions in the kidney beginning at 250 ppm. Microscopic examination of females revealed treatment-related hepatocyte hypertrophy and Kupffer cell pigmentation at 5000 ppm, and increases in severity of hemosiderosis in the spleen and nephrocalcinosis in the kidneys and treatment-related cortical fatty change in the adrenal glands and hepatocyte necrosis beginning at 2500 ppm. **Possible adverse effect:** treatment-related hyaline change in the renal tubular epithelium. NOEL (M)=1.74 mg/kg/day (25 ppm) and (F)=92.5 mg/kg/day (1250 ppm) both based on microscopic findings. **Acceptable**. (Corlett , 9/10/99)

056; 167751; "3-Month Range Finding Study in Mice (Administration in Food)" (Bachmann, M., Novartis Crop Protection AG, Short/Long-term Toxicology, Basle, Switzerland, Study No. 942105, Novartis Nexus No. 704-95, 8/13/96). CGA 293343 tech. (Batch No. KI-4654/18, purity=98.4%) was admixed to the pelleted food at dose levels of 0 (pelleted food), 10, 100, 1250, 3500, or 7000 ppm (0, 1.41, 14.3, 176, 543, and 1335 mg/kg/day, respectively for males and 0, 2.01, 19.2, 231, 626, and 1163 mg/kg/day, respectively for females) and fed to 10 Tif:MAGf (SPF) hybrids of NIH x MAG mice per sex per dose level for 3 months. No treatment-related mortalities occurred. Treatment-related respiratory sounds occurred in males at 3500 and 7000 ppm and in females at 7000 ppm. A treatment-related decrease in mean body weight was observed in males at 7000 ppm. Treatment-related increases in mean relative liver weight in both sexes at 3500 and 7000 ppm and in mean relative testis (both) weight at 7000 ppm, and a treatment-related decrease in mean relative ovary (both) weight at 3500 and 7000 ppm were observed. Microscopic examination revealed a treatment-related increase in incidence and severity of hepatocyte hypertrophy in males beginning at 100 ppm and in females beginning at 1250 ppm and a treatment-related reduction in the number of corpora lutea in the ovaries at 3500 and 7000 ppm. **No adverse effects**. NOEL (M)=1.41 mg/kg/day (10 ppm) and (F)=19.2 mg/kg/day (100 ppm), based on hepatocyte hypertrophy. **Supplemental study** (no clinical biochemistry and no ophthalmological examinations conducted). (Corlett, 9/15/99).

053; 167746; "3-Month Subchronic Dietary Toxicity Study in Beagle Dogs" (Altmann, B., Novartis Crop Protection AG, Short/Long-term Toxicology, Basle, Switzerland, Study No. 942107, Novartis Nexus No. 705-95, 10/15/98). 821. CGA 293343 tech. (Batch No. P. 506006, purity=98.6%) was admixed to the pelleted food at dose levels of 0, 50, 250, 1000, and 2500/2000 ppm (0, 1.58, 8.23, 32.04, and 54.81 mg/kg/day, respectively, for males and 0, 1.80, 9.27, 33.87, and 50.45 mg/kg/day, respectively, for females) and fed to 4 beagle dogs per sex per dose level for a period of 13 weeks. No deaths occurred. No treatment-related clinical signs were observed. Treatment-related decreases in mean body weight and mean food consumption in females at 2500/2000 ppm were observed. Treatment-related decreases in mean cell hemoglobin and mean alanine aminotransferase levels in both sexes at 1000 and 2500/2000 ppm were observed. A statistically significant decrease in mean relative testes weight at 2500/2000 ppm was observed. Microscopic examination revealed moderate bilateral tubular atrophy of the testes in one animal at 2500/2000 ppm, and treatment-related reduced spermatogenesis (bilateral) in the testes, the presence of spermatic giant cells (bilateral) in spermatogenic epithelium of the testes, and immature ovaries (bilateral) and uteri at 2500/2000 ppm. **Possible adverse**

effect: decrease in mean relative testes weight and bilateral tubular atrophy, presence of spermatic giant cells, and reduced spermatogenesis in the testes. NOEL (M)= 32.04 mg/kg/day (1000 ppm, reduced spermatogenesis and testicular atrophy) and (F)= 33.87 mg/kg/day (1000 ppm, immature ovaries and uteri. **Acceptable**. (Corlett , 9/23/99)

052; 167747; "28-Day Exploratory Toxicity Study in Male Rats (Gavage)" (Bachmann, M., Novartis Crop Protection, Inc., Short/long-term Toxicology, Stein, Switzerland, Study No. 932107, Novartis Nexus No. 638-93, 4/25/94). CGA 293343 tech. (Batch No. MF-1846/4, purity> 95%), prepared in 0.5% carboxymethylcellulose and 0.1% Tween 80, was administered 5 times per week for 4 weeks by gavage at daily doses of 0, 100, 300, and 1000 mg/kg to 5 male PRT GAV 01M rats per dose level. One animal at 100 mg/kg died accidentally on day 29. A treatment-related decrease in mean body weight was observed at 1000 mg/kg. Blood chemistry analysis revealed treatment-related increases in mean alkaline phosphatase, aspartate aminotransferase, and gamma-glutamyl transpeptidase levels at 1000 mg/kg were observed. Treatment-related increases in mean relative liver and kidney weights at 300 and 1000 mg/kg were observed. Macroscopic examination revealed treatment-related increased incidences of large livers and renal pelvis dilatation at 1000 mg/kg. Microscopic examination revealed treatment-related increased incidences of hepatocyte hypertrophy at 300 and 1000 mg/kg, hyaline change in the renal tubule at 100 and 300 mg/kg/day, and renal pelvis dilatation and adrenal cortex fatty change at 1000 mg/kg. **No adverse effects**. NOEL (M)<100 mg/kg/day (based on a treatment-related increased incidence of renal tubular hyaline change). **Supplemental study** (no ophthalmological examinations conducted, only male animals used, and animals treated for only 28 days). (Corlett, 8/30/99).

055; 167750; "28-Days Range Finding Study in Rats (Administration in Food)" (Bachmann, M., Novartis Crop Protection, Inc., Short/Long-term Toxicology, Stein, Switzerland, Study No. 942088, Novartis Nexus No. 470-94, 5/5/95). CGA 293343 tech. (Batch No. KGL4654/12, purity> 95%) was admixed to the pelleted food at dose levels of 0 (pelleted food), 100, 1000, 2500, or 10000 ppm (0, 8.04, 81.7, 199, and 711 mg/kg/day, respectively for males and 0, 8.69, 89.3, 211, and 763 mg/kg/day, respectively for females) and fed to 5 Tif:RAIf (SPF) hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level for 4 weeks. No animals died. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight was observed in males at 10000 ppm. Blood chemistry analysis revealed treatment-related increases in mean cholesterol (in males beginning at 1000 ppm and in females at 10000 ppm), urea (in both sexes at 10000 ppm), and aspartate aminotransferase (in males at 10000 ppm) levels. Treatment-related increases in mean relative liver (in both sexes) and kidney (in females only) weights at 10000 ppm were observed. Microscopic examination revealed treatment-related increased incidences of hepatocyte hypertrophy and thyroid follicular epithelium hypertrophy (in males at 2500 and 10000 ppm and in females at 10000), a decrease in hepatocyte glycogen deposition and renal pelvis dilatation (in males at 10000 ppm), renal tubular hyaline change (in males at 1000 and 2500 ppm), and adrenal cortex fatty change (in both sexes at 10000 ppm). **No adverse effects**. NOEL (M)=8.04 mg/kg/day (100 ppm, based on a treatment-related increased
incidence of renal tubular hyaline change), (F)=211 mg/kg/day (2500 ppm, based on treatment-related increases in mean relative kidney and liver weights and increased incidence of hepatocyte hypertrophy). **Supplemental study** (no ophthalmological examinations conducted, only 5 animals per sex per dose used, and animals treated for only 28 days). (Corlett, 9/2/99)

52691-081 167699 "Assessment of Replicative DNA Synthesis in the Course of a 28-Day Oral (Feeding) Toxicity Study in Male Rats" (Persohn, E., Toxicology Services/Cell Biology, Novartis Crop Protection, Basle, Switzerland). In a previous 28-day toxicity study in male rats (DPR# 52691-052:167747; Novartis study # 932107), increased liver weights in rats treated with 300 and 1000 mg/kg of test chemical accompanied by minimal to moderate hepatocellular hypertrophy and moderate proliferation of smooth endoplasmic reticulum was observed. One high-dose animal also showed pronounced nuclear alterations in hepatocytes (vesicular nuclei and prominent, large nucleoli) as well as increased mitotic activity. Liver sections from rats administered CGA-293343 Technical (Batch # P.506006, purity 98%) in the feed for 28 days at doses of 0, 100, 1000, 2500 and 10000 ppm (DPR# 52691-055:167750; Novartis study # 942088) were used to assess a possible effect of CGA 293343 on

replicative DNA synthesis. Heptocellular proliferation was tested using four liver tissue blocks (fixed and embedded in paraffin) from each animal; initially, two liver blocks from each animal of the control and 10000 ppm dose group were processed using immunohistochemical staining to detect proliferating cell nuclear antigen (PCNA). Three sections per block were incubated with monoclonal anti-PCNA antibody clone PC10 and further processed with an Avidin Biotin Alkaline Phosphatase Detection Kit. Cells in S-phase of the cell cycle were identified by uniform dark red nuclear staining for PCNA; there was no indication for a treatment-related increase in the fraction of DNA synthesizing hepatocytes in S-phase. It was concluded that CGA 293343 did not stimulate hepatocyte cell proliferation in male rats at dietary levels of 10000 ppm (711 mg/kg b. wt.) for 28 days. Supplemental study. Kellner, 10/4/99.

057; 167752; "28-Day Range Finding Study in Beagle Dogs" (Altmann, B., Novartis Crop Protection AG, Short/Long-term Toxicology, Basle, Switzerland, Study No. 942106, Novartis Nexus No. 473-94, 6/19/96). CGA 293343 tech. (Batch No. KI-4654/18, purity=98.4%) was admixed to the pelleted food at dose levels of 0 (pelleted food), 300, 1000, or 3000 ppm (0, 10.0, 31.6, and 47.7 mg/kg/day, respectively, for males and 0, 10.7, 32.6, and 43.0 mg/kg/day, respectively, for females) and fed to 2 beagle dogs per sex per dose level for 28 consecutive days. One male at 3000 ppm was found dead on day 15. No treatment-related clinical signs were observed. Treatment-related decreases in mean body weight and mean food consumption in both sexes at 3000 ppm were observed. A treatment-related decrease in mean relative thymus weight in both sexes at 3000 ppm was observed. Microscopic examination revealed treatment-related pigmentation in the Kupffer cells, and atrophy of the thymus and of the marginal zone of the splenic white pulp. **No adverse effects**. NOEL (M)=31.8 mg/kg/day (1000 ppm) and (F)=32.6 mg/kg/day (1000 ppm), based on decreased body weight and food consumption, and microscopic findings. **Supplemental study** (only 2 animals per sex per dose used and animals treated for only 28 days). (Corlett, 9/16/99).

(Dermal)
058; 167754; "28-Day Repeated-Dose Dermal Toxicity Study in Rats" (Gerspach, R., Novartis Crop Protection AG, Short/long-term Toxicology, Basle, Switzerland, Study Number 942116, Novartis Nexus No. 511-96, 10/8/96). 822. CGA 293343 tech. (Batch No. P. 506006, purity=98.6%), suspended in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80, was applied to the clipped skin of 5 Tif: RAIf (SPF) hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose at dose levels of 0 (vehicle only), 20, 60, 250, or 1000 mg/kg/day for 6 hours per day 5 days per week for 4 weeks using an occlusive dressing. No animals died. No treatment-related clinical signs or signs of local irritation were observed. Dose-related increases in mean serum glucose and mean serum triglycerides in females at 250 and 1000 mg/kg/day were observed. Also, a treatment-related increase in mean serum alkaline phosphatase level was observed in females at 250 and 1000 mg/kg. Microscopic examination revealed treatment-related hyaline change in renal tubules of males at 1000 mg/kg/day and treatment-related minimal-moderate inflammatory cell infiltration in the liver of females at 60, 250, and 1000 mg/kg/day. **Possible adverse effect:** treatment-related hyaline change in the renal tubules of high dose males. NOEL (systemic, M)=250 mg/kg/day based on hyaline change in renal tubules, NOEL (systemic, F)=60 mg/kg/day based on elevated alkaline phosphatase and abnormal liver histology, NOEL (dermal, M/F)=1000 mg/kg/day based on no signs at HDT. **Acceptable.** (Corlett, 9/27/99).

METABOLISM STUDIES

**52691-144, -077, -145 167788, 167695, 167789 "Absorption, Distribution and Excretion of [Thiazol-2-^{14}C] and [Oxadiazin-4-^{14}C] CGA-293343 in the Rat" (Muller, T., 851-Animal Metabolism, Novartis Crop Protection, Basle, Switzerland, Project # 027AM01, 027AM09, 027AM02, Report 11/96, 8/15/96). Non-radiolabeled: CGA 293343 (Batch # KI-4654-18 and AMS 780/101, purity >98% and >99%, respectively); Radiolabeled: [Thiazol-2-^{14}C] CGA-293343 (Batch #Ko-73.1A and Ko-73.2A-1, specific activity 68.9 and 57.3 µCi/mg, respectively, purity of >97%) and [Oxadiazin-4-^{14}C] CGA-293343 (Batch Ko-75.2A-2 and Ko-75.2A-3, spec. act. of 87.0 and 84.6 µCi/mg, purity >96%) were administered to 4 or 5 Tif:RAI f (SPF) rats/sex/dose at 0.5 mg/kg, to 5 rats/sex at 0.5 mg/kg (after 14 days of unlabeled CGA 293343) and to 5 rats/sex at 0.5 or 100 mg/kg by oral gavage or

I.V. Supplemental study (-077:167695) used 3 groups of 4 male Tiflbm:MAG (SPF) mice receiving [Thiazol-2-^{14}C] CGA 293343 for 14 days at 118 mg/kg to determine excretion and metabolic fate in mice. In rats, the dose was rapidly absorbed from the G.I. tract into the general circulation with maximum blood levels (tc_{max} [h]) achieved 1 to 4 hours independent of the radiolabel site, dose level or sex. C_{max} ranged from 0.17 to 0.20 ppm (low dose) and 33 to 43 ppm (high dose) and levels declined rapidly ($tc_{max/2}$ about 8 hours). Bioavailability 0.6 to 0.8 (males) and 0.7 to 0.9 (females) indicated sizable oral absorption. Absorbed material was primarily excreted via the urine (approximately 90%) compared to about 4% in feces within 24 hours. The preponderance of fecal elimination originated from biliary excretion. Half-lives in all tissues ranged from 2 to 6 hours. Comparison of metabolite patterns in mice and rats indicated that the major metabolic pathways were similar. Biotransformation in mice was 30-60%, with CGA-322704 the major urinary metabolite. The formation of polar metabolites in urine was greater in mice (4.7-8% of dose) than rats (0.3% of daily dose). **Acceptable.** (Kellner, 9/30/99).

SUPPLEMENTAL STUDIES

187; 172709; "Liver Tumor Formation in Mice by Thiamethoxam (CGA-293343) - Implications for Human Risk Assessment "; (E. Weber, *et al*; Novartis Crop Protection AG, Basle, Switzer-land; Novartis No. 1199-99; 12/7/92). This report provides a risk assessment of liver tumors in Tif: MAGf (SPF) mice fed for 18 months with 5, 20, 500, 1250 or 2500 ppm thiamethoxam (CGA-293343 Technical, 98% purity), arguing that the mechanisms involved with their formation are species specific and threshold in nature, and therefore justify the use of margin of exposure methods for risk assessment rather than linear low-dose extrapolation. The key points of the argument are: thiamethoxam shows a lack of mutagenicity in standard assays; carcino-genicity was observed only in the mouse (not in rat or dog); and the postulated mechanism of action involves hepatocellular apoptosis and necrosis followed by regenerative hepatocyte proliferation, which is unlikely to occur in humans. A risk assessment method is proposed based on the LED10 for hepatocellular hypertrophy or single cell necrosis and using a margin of exposure of 300. The calculated RfD was 0.0017 mg/kg/day based on 0.5 mg/kg/day human LED10. **Supplemental.** (Duncan, 7/31/00)